TO: Documents Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Docket No. 99D-3082
International Conference on Harmonisation; Choice of Control Group in Clinical Trials

FROM: Statistical Data Analysis Center
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We, individually and as a group, have reviewed this draft guidance carefully, held a working group meeting and have prepared the following comments.

General Comments

- The current FDA document is hard to follow.

- Organizationally, we recommend that Section 1.4: Purposes of Clinical Trials come before Sections 1.2: Purpose of Control Group and 1.3: Types of Controls.

- We believe clinical trials, both superiority and noninferiority, are more properly viewed in terms of hypothesis testing, not estimation. From this perspective,
  a superiority trial is a test of the null hypothesis of H_0: treatment effect ≤ 0 (nonsuperiority) vs. the alternative hypothesis H_1: treatment effect > 0 (superiority), and
  a noninferiority trial is a test of the null hypothesis H_0: treatment effect $\leq \delta$ (inferiority) vs. the alternative hypothesis H_1: treatment effect $> \delta$ (noninferiority) for a prespecified $\delta < 0$.

  There is, of course, a one-to-one relationship between a hypothesis test and a confidence interval for the "treatment effect," and estimation of the "treatment effect" is an important *secondary* outcome of the clinical trial. However, we believe that the *primary* outcome of a clinical trial is acceptance or rejection of the prespecified null hypothesis and that viewing clinical trials as hypothesis tests will clarify both the similarities and differences between superiority and noninferiority trials.

- The draft guidance distinguishes between two types of trials in Section 1.4 – efficacy trials (either superiority or noninferiority) and comparative (equivalence) trials. We suggest further emphasizing the difference between superiority trials and noninferiority trials as evidence of efficacy by including subsections distinguishing between three types of trials – superiority trials, noninferiority trials as evidence of efficacy and comparative (equivalence) trials.

- The choice of control group is primarily driven by ethical, not scientific, considerations. That is, in most settings, if it is ethical, the preferred trial is a superiority trial (best care + new treatment vs. best care). Noninferiority trials (best care + new treatment vs. best care + old treatment) to show efficacy are only used when it is unethical to conduct a placebo-controlled superiority trial.

- In the context of hypothesis testing, bias in a randomized clinical trial refers to systematic factors which invalidate tests of hypotheses, in particular, factors which inflate the type I error rate. In a superiority trial, errors which make the treatment groups look similar do not inflate the type I error rate and, thus, do not raise questions about a finding of superiority. (On the other hand, they make it difficult to interpret a failure to find superiority.) In contrast, in a noninferiority trial, such errors do inflate the type I error rate, and, thus, do call into question a finding of noninferiority.

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- We are skeptical of noninferiority trials intended to show efficacy. As is made clear in the draft ICH E10 document, this presupposes that the active control has some minimal "treatment effect". We contend that randomized controlled clinical trials are not well suited for the estimation of "treatment effects", and, therefore, conclusions of efficacy from noninferiority trials may not be compelling.

- Given the previous point, it should be stressed that, if at all possible, randomized clinical trials should be designed as superiority trials since attempting to demonstrate efficacy via a noninferiority trial is not likely to be as convincing. While this view is implicit in much of the discussion, we believe that it is an important point and should be stated explicitly.

- We think that a distinction must be drawn between a conclusion of noninferiority and a conclusion of noninferiority being used as evidence of efficacy. It is possible to conclude a new drug is noninferior to an active control based solely on the results of a well-designed, well-conducted randomized clinical trial. In contrast, a conclusion of noninferiority, in one trial or in many trials, can only provide indirect evidence of efficacy. Thus, it is possible to conclude noninferiority and yet not be able to claim efficacy. Again, this view is implicit in the discussion of active controls, but we believe it should be stated unequivocally.

- We also note that, in noninferiority trials intended to show efficacy, the role of previous trials of the active drug versus placebo is similar to the role of historical controls in a historical control trial. Thus, many of the known weaknesses of historical control trials will also apply to noninferiority trials intended to show efficacy. In particular, methods designed to impute the effect of active control (relative to placebo) in the current trial depend heavily on the relevance of the historical data to the present day.

Specific Comments

Quoted, italicized text is quoted from the guidance document. (n,m) means the nth paragraph, mth sentence. Our comments are in plain text.

1.2.2 Blinding

- (1,2) *"... both subjects and investigators (including analysts of data, sponsors, other clinical trial personnel) are unaware of each subject's assigned treatment ..."*

  In our opinion, data analysts perhaps should not be completely blinded. Indeed, interim analyses of study data will require (partially) unblinded data analysts. Instead, the primary analyses should be prespecified in the protocol (and/or analysis plan) and all subjects' results included in the primary analysis, so there is little analyst discretion to change the analysis or no discretion to exclude a subject's results.

1.3.1 Placebo Concurrent Control

"Placebo" is only defined implicitly as (1,1) *"identical-appearing inactive treatment"*. Technically, a placebo is an "inert or innocuous substance". In the context of this document, "placebo" ought to include sham treatments or procedures as well and should be taken to mean best care + "placebo".

(1,6) Regression to the mean is not cited as a possible influence on disease progression.

1.3.5 External Control (Including Historical Control)

(1,5) *"Baseline-controlled" studies* are highly susceptible to regression to the mean.

1.5 Sensitivity-to-Drug Effects and Assay Sensitivity of Studies Intended to Show Noninferiority/Equivalence

- (1,2-4) *"A demonstration of efficacy by showing noninferiority/equivalence ... rests on the assumption that the active-control drug will have an effect of a defined size .... If these assumptions are incorrect, an erroneous conclusion that a drug is effective may be reached because a trial seeming to support noninferiority will not in fact have done so."*

  Although we agree with the underlying sentiment of this statement, we disagree with the final clause *"because a trial seeming to support noninferiority will not in fact have done so".* The trial has, in fact, shown noninferiority, but it has not shown efficacy. This again highlights the large distinction between noninferiority and noninferiority as evidence of efficacy.

- (2,7) *"... in a similarly well-designed and conducted noninferiority trial, there will be an ability not to find an ineffective agent to be noninferior"*

  This is stated as a negative. It would be clearer if stated in the affirmative such as "a similarly well-designed and conducted noninferiority trial will have a low probability of finding an ineffective agent to be noninferior, i.e., a low type I error rate."

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